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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,595	06/07/2002	Albrecht E. Sippel	WEICKM 14	5887
23599	7590	09/21/2006	EXAMINER	
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			GAMEETT, DANIEL C	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/869,595

Applicant(s)

SIPPEL ET AL.

Examiner

Daniel C. Gamett, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07/10/2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 10, 15-20, 22-28, 30-37, 39-43, 61-63, 67-70 and 79-84 is/are pending in the application.
- 4a) Of the above claim(s) 11-13, 29, 38, 44-60, 64-66, 71, and 74-78 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1, 2, 15-18 and 83 is/are allowed.
- 6) ☒ Claim(s) 3, 4, 10, 19, 20, 22, 30, 33, 39, 62, 82 and 84 is/are rejected.
- 7) ☒ Claim(s) 23-28, 31, 32, 34, 37, 40-43, 61, 63, 67-70 and 79-81 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The amendments of 07/10/2006 have been entered in full. Claims 5-9, 14, 21, and 72-73 are cancelled. Claims 11-13, 29, 38, 44-60, 64-66, 71, and 74-78 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-4, 10, 15-20, 22-28, 30-37, 39-43, 61-63, 67-70, and 79-84 are under examination.
2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

4. Rejection of claim 10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. The claim is still self-contradictory in reciting a third domain that is both constitutively active and regulated. Applicant's dilemma of seeking to recite a domain known in the art as "constitutively active ras" in a context where the activity is no longer constitutive, but rather is regulated by ligand binding, is understood. The essential feature of the claimed ras is that it shows activity irrespective of the presence of guanine nucleotide exchange factors (specification, page 13, lines 25-28). This description (or a more succinct equivalent, if possible) could be substituted for "constitutively active ras" in order to obviate this rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. Claims 30 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are self-contradictory in reciting a third domain that is both constitutively active and regulated.
6. Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 62 recites the limitation "fusion protein as claimed in claim 36, where the fusion protein comprises a third domain which is able to activate the inactive or inactivatable signal pathway connected to a Ras protein in the cells when there is lack of binding...to the second domain." There is insufficient antecedent basis for this limitation in the claim. This mode of action is not recited for the fusion protein in claim 36, nor in any of the claims from which claim 36 depends.
7. Claim 84 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 84 recites the limitation "kit of claim 10". There is insufficient antecedent basis for this limitation in the claim. Claim 10 does not recite a kit.
8. Claims 3, 4, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 3 is drawn to an embodiment of the fusion protein of claim 1 wherein the third domain can be complexed by a multiprotein complex attaching to the fusion protein in such a way that the third domain is unable to exert its activity to activate a signal pathway connected to a Ras protein in a cell; claim 20 is drawn to a cell expressing such a fusion protein. Consistent with the state of the art, the specification (page 11, lines 11-39) teaches that nuclear receptors exist in the cells as inactive multiprotein complexes. The binding sites for the multiprotein complexes are adjacent to or overlapping with the ligand-binding domain. Therefore, it is expected that proteins intrinsic to the cell would complex with the *second* domain of the claimed fusion protein and that activity of the fusion protein would be regulated similarly to nuclear receptors, that is, the complexes are displaced upon ligand binding leading to receptor activation. Claims 3 and 19, however, recite the *third* domain being bound to multiprotein complexes. The elected species to of the third domain of the fusion protein is Ha-ras (L61). Non-elected species of the third domains include guanine nucleotide exchange factors such CDC25 or SOS. The signaling activity of ras is known to be regulated by its intrinsic GTPase function, GTPase activating proteins, and by guanine nucleotide exchange factors, which in turn may be regulated by phosphorylation and by interaction with phosphorylated molecules such as Grb2 (The Cell: A Molecular Approach, 2nd Edition, 2000, by Geoffrey M. Cooper; figure 13.34; Thevelein *et al.*, Molecular Microbiology Volume 33 Page 904-918, September 1999; see figure 1). The prior art provides no suggestion that ras, CDC25, or SOS proteins ever exist in cells as inactive protein complexes that may be activated by displacement of negatively regulatory proteins. The conceptual

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basis for these claims (specification, page 9, lines 19-37) is completely hypothetical, and no evidence or example is provided. Therefore, the specification does not enable a skilled artisan to make or use a fusion protein that functions in the claimed manner.

9. Claims 19 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a eukaryotic cell as claimed in claim 19, does not reasonably provide enablement for a prokaryotic cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claim 19 is drawn to a cell comprising a fusion protein as claimed in claim 1; the claim redundantly recites the properties of the protein, apparently to emphasize that the fusion protein is functional within the cell. The claimed protein must be able to activate a ras pathway where there is binding of a ligand to the second domain. Prokaryotic cells do not have the components of a ras pathway (see for example Cooper, figure 13.34, or Thevelein *et al.*, figure 1), nor do they intrinsically have targets, such as transcription factors or cell cycle proteins, that could mediate a detectable response to ras activity. Constructing a prokaryotic cell as in claims 19 or 22 would require undue experimentation.

10. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 39 is drawn to an assay comprising contacting a test substance with cells as claimed in claim 23; the cells are

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(redundantly) recited in (a) to contain a fusion protein comprising a third domain which is able to activate the inactive signal pathway connected to a Ras protein only when there is binding of ligand to the second domain. Part (c) of the method recites, “where detection of the activation of the signal pathway connected to a Ras protein in the absence of the test substance and the inactivity of the signal pathway connected to a Ras protein in the presence of the test substance indicates the ability of the test substance to bind to the second domain of the fusion protein.” This result is impossible. According to the definitions given in (a), there can be no activation of the signal pathway connected to a Ras protein in the absence a ligand to bind the second domain. The recited fusion protein is positively regulated by ligand binding at the second domain, step (c) purports to detect a negative regulator.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claim 82 is rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. Claim 82 appears to be identical to claim 1, except that the final limitation of claim 1, “but when there is binding of ligand to the second domain of said fusion protein, said signaling pathway is activated”, is not included in claim 82. Therefore, claim 82 recites a fusion protein with three domains, indicates something that it cannot do, but fails to indicate anything that it *can* do. The specification does not assert a utility for such a protein and;

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therefore, the question of whether any asserted utility is specific, substantial, or credible, could not be addressed.

Conclusion

13. Claims 1,2,15-18, and 83 are allowable.

14. Claims 3,4,10, 19, 20, 22, 30, 33, 39, 62, 82, and 84 are rejected.

15. Claim 23-28,31-37, 40-43, 61, 63, 67-70, and 79-81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

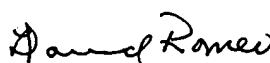
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Applicant's attention is directed to MPEP § 502.03, regarding the use of Internet e-mail. Subsection V states in part that, "Internet e-mail shall **NOT** be used to conduct an exchange of communications similar to those exchanged during telephone or personal interviews unless a written authorization has been given under Patent Internet Usage Policy Article 5 to use Internet e-mail. In such cases, a paper copy of the Internet e-mail contents **MUST** be made and placed in the patent application file...in the same manner as an Examiner Interview Summary Form is entered."

DCG

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12 September 2006


DAVID S. ROMEO
PRIMARY EXAMINER